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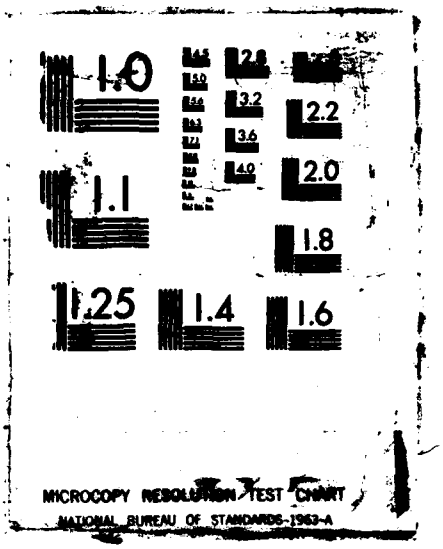
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STANFORD UNIVERSITY
STANFORD, CA 94305

NEUROREGULATORS AND STRESS

1979 - 1986

FINAL REPORT

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Principal Investigator

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Final Report

Jack D. Barchas, M.D.
Principal Investigator

this paper describes the

INTRODUCTION

The work accomplished under our ongoing ONR contract has been in four areas: I) Characterization and Neurobiology of Biological Peptides; II) Brain with Peripheral Catecholamines and the Stress Response; III) Mass Spectrometric Analytical Neurochemistry; and IV) Sociophysiology of Social Relationships. The program report and list of publications provides a sense of the areas and the exciting progress which has been made in each of the areas. The ONR support was enormously valuable.

I. CHARACTERIZATION AND NEUROBIOLOGY OF BIOLOGICAL PEPTIDES

One of the most exacting dimensions of our work has included isolation and characterization of neuroactive peptides. In particular we have focused on some of the morphine-like peptides in terms of identifying substances in the brain. We have characterized the major opioid-like immunoreactive material in the shark brain; isolated a major dynorphin fragment in the bovine caudate; and studied the response of the dynorphin peptides to dehydration stress. In addition, we have been conducting studies and prepared reviews dealing with opioid peptides in the adrenal-pituitary axis.

Characterization of Endorphins from the Shark

In mammals it is known that pro-opiomelanocortin (POMC) contains the pituitary peptides adrenocorticotropin (ACTH) and β-lipotropin (β-LPH). ACTH can be further processed to yield α-melanocyte stimulating hormone (α-MSH) and corticotropin-like intermediate lobe peptide (CLIP), while β-LPH can be further processed to β-melanocyte stimulating hormone (β-MSH) and the opioid peptide β-endorphin (β-EP). A similar POMC molecule has been described in the amphibians Xenopus laevis and Rana ridibunda and also in the teleost Onchorynchus keta (chum salmon), where the partial mRNA sequence of the POMC gene has been reported.

Although proposed to exist in other lower vertebrates, no POMC-like molecule has been reported in the cartilaginous fishes. In the case of the dogfish shark Squalus acanthias, amino acid sequence data for the presumed POMC products ACTH, α-MSH, CLIP, and β-MSH have been published, but confirmation of the presence of β-LPH and β-EP-like molecules is lacking except for a single report describing the detection of pituitary derived β-EP-like immunoreactivity. We sought to clarify this situation and report herein a detailed characterization of the endorphins from the dogfish shark. Our results, in conjunction with previous studies on shark pituitary, indicate that this elasmobranch has all the major POMC-related end products found in mammals and adds insight into the evolutionary development of opioid-like molecules.

The immunoreactive material in shark pituitary extracts was purified to apparent homogeneity by reverse-phase high-performance liquid chromatography and subsequently characterized by amino acid analysis, Edman degradation and fast atom bombardment mass spectrometry. The largest opioid-like peptide

isolated contained 30 amino acids and showed 80% homology with salmon endorphin-II but less than 50% homology with human β-endorphin. Three structural variants of this molecule were also characterized. These variants were shown to be shorter N-terminal fragments, two of which corresponded to cleavage products at the single basic residues arginine[11] and lysine[26]. Cleavage at a single lysine residue has not been reported for posttranslation processing of β-endorphin in mammals and could represent a modification seen only in lower vertebrates. The remaining fragment corresponded to a loss of 3 residues from the C-terminus of the parent molecule. No α-N-acetylated peptides were detected. These results provide the first unequivocal confirmation of β-endorphin in an elasmobranch and provide evidence of novel N-terminal variants of β-endorphin.

Isolation of an Endogenous C-Terminal Fragment of Dynorphin from Bovine Brain

Antibodies have been raised to a synthetic peptide corresponding to the C-terminal 15-amino acid residues of prodynorphin, the common precursor to the neo-endorphins and dynorphins. The amino acid sequence of the antigen was based on the sequence deduced from mRNA isolated and cloned from porcine hypothalamus. Using a radioimmunoassay developed from these antibodies we have isolated an endogenous prodynorphin C-fragment from bovine caudate nucleus. The isolated peptide displayed characteristics on gel filtration similar to those of synthetic prodynorphin C-fragment predicted from the porcine mRNA sequence but had low cross-reactivity in the radioimmunoassay. Sequencing and amino acid analysis showed a substitution of serine for asparagine at position 6 in the porcine sequence. Dynorphin B (rimorphin), which is adjacent to prodynorphin C-fragment in the precursor, was isolated from the same extract. Amino acid analysis and elution position on a gel filtration column confirmed its structure as that previously characterized from bovine pituitary extracts. The release of prodynorphin C-fragment and the C-terminus of dynorphin B from the porcine precursor would require cleavage at a single arginine residue. However, a terminal arginine was not present on either of these prodynorphin peptides isolated from bovine caudate. The data would suggest that processing at a single arginine residue results in elimination of the arginine, a feature in common with processing at paired basic residues.

Effects of Dehydration on Dynorphin-Derived Peptides

It is well established that under conditions of chronic stimulation of the hypothalamo-neurohypophyseal system, such as dehydration, there is a depletion of the neurohypophyseal hormones vasopressin and oxytocin from the posterior lobe of the pituitary gland. Vasopressin and oxytocin are produced in neurons of the supraoptic and paraventricular nuclei of the hypothalamus and are stored in the posterior lobe of the pituitary gland from which they are released. A similar neuronal pathway between enkephalin-immunoreactive (ir) neurons in the magnocellular hypothalamic nuclei and enkephalin-ir terminals in the pars nervosa has been detected. The suggestion was made that this enkephalin immunoreactive material could be released with vasopressin and oxytocin, or alternatively, that these enkephalinergic fibers could somehow interact with the secretion of neurohypophyseal hormones.

Enkephalins have been demonstrated to co-exist with oxytocin and vasopressin in nerve terminals of the rat neurohypohysis, and more recently it has been reported that dynorphin and vasopressin are colocalized in hypothalamic magnocellular neurons and in rat pituitary neurosecretory vesicles. These findings suggest that in response to dehydration, a stimulus known to induce vasopressin release, dynorphin and related peptides may be released in the pituitary concomitantly with vasopressin. In support of this corelease are experiments by Hollt which demonstrated significant decreases in both ir-dynorphin and ir-vasopressin after dehydration.

Cleavage of prodynorphin at double basic "processing signals" gives rise to three opioid peptides in brain: dynorphin A(1-17) (Dyn A); dynorphin B-29; and α-neo-endorphin (α-neo). The dynorphin A region has been shown to be processed in many brain regions by a single arginine cleavage process to dynorphin A(1-8) (Dyn 1-8). α-Neo is processed in some brain regions to β-neo-endorphin (β-Neo) by removal of a single lysine residue. All these peptides contain a leu-enkephalin at the N-terminus which could be released by cleavage at double basic residues.

The present study was undertaken to investigate the possibility that dehydration may alter the absolute concentrations as well as the ratios of prodynorphin processing products stored in the posterior-intermediate lobe of the pituitary and hypothalamus.

The present study demonstrates that the concentration of immunoreactive prodynorphin derived peptides in the neuro-intermediate lobe of the pituitary are reduced in response to saline dehydration, whereas food-deprivation does not modify these concentrations. Rats dehydrated under similar conditions show a highly significant decrease (94%) in the concentration of ir-vasopressin in the neurointermediate pituitary. These results strongly indicate that prodynorphin products are released in the pituitary concomitantly with vasopressin during the antidiuretic response. Our results show a small increase in hypothalamic concentrations of immunoreactive prodynorphin derived peptides. This increase may be due to changes in the rate of biosynthesis of the molecules or it could reflect an alteration in processing, release, degradation, or a combination of these.

In trying to elucidate the tissue response to dehydration, it is useful to calculate the molar ratios of prodynorphin cleavage products. The prodynorphin product β-neo is thought to be generated from α-neo by removal of the C-terminal lysine by a carboxypeptidase B-like enzyme. This may be a slow conversion, as a proline residue precedes the bond to be cleaved. We postulate that dehydration may stimulate release of the prodynorphin products before the enzyme has a chance to cleave α-neo into β-neo and thereby the ratio of these stored peptides is altered. Indeed, the ratio of α-neo:β-neo is significantly increased in dehydrated rat posterior-intermediate lobe from 0.43 to 1.15. In the hypothalamus, the molar ratio of α-neo:β-neo was not significantly altered upon dehydration.

The C-terminus of Dyn 1-8 is released from the prodynorphin precursor by cleavage at a single arginine residue. Dyn A is formed by a cleavage at the paired basic residues, lysyl arginine. The ratio of Dyn A:Dyn 1-8 is reduced from 0.65 in control rats to 0.25 in dehydrated rats, suggesting that the

ability to generate Dyn 1-8 is not impaired during response to dehydration. This is in direct contrast to the increase seen in the α-neo:β-neo molar ratio, which suggests that the ability to generate β-neo is impaired during dehydration. The possible physiological significance of these changes in stored prodynorphin products is at present unknown.

As dynorphin and opioid peptides have been implicated in stress responses, it is possible that the reduction and possible altered processing of ir-pro-dynorphin products seen in the present study are due to a stress-related effect. In order to address this question, a food-deprived stress-control group was run. We found no significant changes in tissue concentrations of ir-pro-dynorphin products in rat pituitary and only a significant decrease in ir-β-neo in rat hypothalamus. This result suggests that the reduction in ir-pro-dynorphin derived peptides is primarily due to the antidiuretic response and is not a general stress-related effect.

Recent colocalization evidence points to the possibility that the opioid peptides in the oxytocin and vasopressin systems are derived from different opioid precursor molecules. Both leu- and met-enkephalin immunoreactive material was seen in oxytocin terminals, but only leu-enkephalin immunoreactivity was seen in vasopressin terminals. It has now been shown that leu-enkephalin can be generated from the prodynorphin molecule as well as the pro-enkephalin molecule. This study shows a concurrent reduction of leu-enkephalin with other prodynorphin peptides. These results would indicate that part of the ir-leu-enkephalin found in the pituitary is derived from the prodynorphin molecule.

This study points to a linkage of prodynorphin derived molecules with the antidiuretic response. The original finding that opioid peptides were colocalized with vasopressin and oxytocin in nerve terminals led to the suggestion that the opioid peptides played a regulatory role in the antidiuretic response. The significant reduction in prodynorphin derived peptides induced by dehydration and the altered ratios of stored products seen among these peptides suggests that some of these compounds may play part of this regulatory role.

II. BRAIN AND PERIPHERAL CATECHOLAMINES AND THE STRESS RESPONSE

From its initiation, almost two decades ago, our ONR program has included a component dealing with catecholamines and stress. An early part of that work was the Bennett Award. In the interim we have developed improved methods of assessing peripheral catechols as well as extended our work on brain epinephrine, a relatively unstudied but potentially quite important substance in the stress response. A study that has received an excellent response dealt with catecholamine secretion as a function of perceived coping self-efficacy. That study combines chemical methods and psychological research.

Effects of Acute and Chronic Stress on Brain Epinephrine

Epinephrine in the central nervous system may influence anterior pituitary hormone release, sympathetic nervous system regulation and the response to

intracranial reward. With such a wide range of influence on physiological and behavioral functions it is not surprising that epinephrine neurons in the central nervous system are extremely responsive to stress. The highest concentration of epinephrine, in both rats and man, is found in the hypothalamus, a region of the brain critical to stress responding and pituitary hormone regulation.

In the rat brain it is known that phenylethanolamine-N-methyl transferase (PNMT) activity is altered by both acute and repeated stress. After acute stress, hypothalamic epinephrine concentrations are decreased by a greater percentage than dopamine, norepinephrine, and serotonin concentrations. During the contract we have examined the effects of both acute and chronic stress on rat brain hypothalamic epinephrine concentrations and turnover. In addition, we have performed experiments to determine the effect of nicotinic stimulation on hypothalamic epinephrine concentrations and turnover in acute and chronically stressed rats. In all our experiments we have used a 30 minute oscillation stress consisting of placing unrestrained rats on a 12 x 18 inch platform which oscillates horizontally at ≈3 Hz.

In rats exposed to acute oscillation stress, hypothalamic epinephrine concentrations were decreased ≈30% immediately following the stress and returned to baseline in 24 hours. Studies with the PNMT inhibitor 2-chloro-3-trifluoromethyl-α-benzylamine (CTFMB) and the dopamine-β-hydroxylase (DBH) inhibitor fusaric acid indicate there is an increased epinephrine turnover under acute stress. When rats are exposed to repeated oscillation stress, 30 minutes oscillation stress/day, and epinephrine concentrations measured 24 hours after the last stress, epinephrine concentrations are significantly elevated after seven days of stress and are increased ≈25% over baseline by 21 days. Synthesis inhibition studies indicate a decreased epinephrine turnover under chronic stress.

The finding that chronic stress decreases epinephrine turnover in rats is particularly interesting since a relationship between stressful life events and human depression has previously been noted. Epinephrine concentrations have been reported to be decreased in the cerebrospinal fluid of depressed patients. These findings suggest that central epinephrine may be involved in affective disorders and stress responding.

Both nicotine and acute stress decrease hypothalamic epinephrine concentrations and increase epinephrine turnover. The effect of nicotine on epinephrine concentration and turnover can be blocked by the nicotinic antagonist mecamylamine. To examine if nicotinic stimulation was responsible for the acute stress-induced changes in epinephrine concentration and turnover, we injected rats with mecamylamine prior to an acute oscillation stress and examined epinephrine concentrations and turnover. Mecamylamine failed to prevent the acute stress induced changes in epinephrine concentration and turnover. This finding indicates that the acute stress-induced changes in epinephrine occur independently of nicotinic receptor activation.

We have also compared the effect of nicotinic stimulation on epinephrine concentrations in animals exposed to 7 days of oscillation stress (30 minutes/day)

versus unstressed animals. In unstressed rats nicotine decreased epinephrine concentrations ≈20% in one hour. Nicotine produced a significantly greater decrease in epinephrine concentration in rats exposed to repeated stress, the last stress administered 24 hours prior to nicotine, epinephrine concentrations being decreased ≈40% from baseline. These findings suggest that although nicotinic stimulation may be uninvolved in the acute stress induced changes in epinephrine turnover, chronic stress may produce a supersensitivity of nicotinic receptors which may interact with epinephrine neurons.

Epinephrine Accumulation in Rat Brain after MAO Inhibition

The existence of multiple forms of monoamine oxidase (MAO) and of selective inhibitors toward these multiple forms has been known for several years. MAO inhibitors have been used effectively for many years in the treatment of depression. Most clinically approved MAO inhibitors, however, demonstrate little selectivity towards the two forms of MAO. Recent evidence from clinical trials suggests that selective inhibition of the A form of MAO may have more antidepressant efficacy than inhibition of MAO Type B. It has been demonstrated in the rat that chronic regimens of selective MAO inhibitors can be chosen at dosages to maintain effective selectivity over several weeks. In light of the possible clinical significance of selective MAO inhibition, a study was undertaken to determine the effects of chronic administration of selective inhibitors of both the A and B forms on regional rat brain catecholamines, serotonin and their metabolites.

Selective inhibitors chosen for this work were pargyline (1 mg/kg i.p.), which has been shown to be a selective inhibitor of MAO Type B over a three-week period and Lilly 51641 (0.5 mg/kg i.p), a potent selective MAO Type A inhibitor.

Concentrations of biogenic amines and metabolites were measured in regions of rat brain following administration of MAO inhibitors for 21 days. Epinephrine concentrations were increased from 350-500% following chronic administration of LY 51641, a selective inhibitor of MAO type A. Norepinephrine, dopamine and serotonin showed much less relative accumulation.

The marked relative accumulation of epinephrine may be related to the efficacy of inhibitors of MAO type A in the treatment of depression. It raises the theoretical possibility, when combined with our studies dealing with brain epinephrine changes in stress, that treatment with MAO Type A inhibitors may be useful in dealing with certain types of stress states such as cold water.

Catecholamine Secretion as a Function of Perceived Coping Self-Efficacy

The present research tested the hypothesis that perceived coping self-efficacy mediates the effects of environmental events on a catecholamine secretion. Differential levels of perceived self-efficacy were induced in phobic subjects through modeling. Their level of catecholamine secretion was then measured as they were presented coping tasks in their high, medium, and low ranges of perceived self-efficacy. High perceived self-efficacy was accompanied by low

levels of plasma epinephrine and norepinephrine during interaction with a phobic object, whereas moderate perceived self-inefficacy gave rise to substantial increases in plasma catecholamines. Both catecholamines dropped sharply when phobics declined tasks for which they judged themselves completely inefficacious. In contrast, DOPAC was released maximally by mere apperception of task demands that phobics regarded as overwhelming their coping capabilities. After perceived self-efficacy was strengthened to the maximal level by participant modeling, all of the tasks were performed without any differential catecholamine responses.

Results of the present study lend support to the view that perceived coping self-efficacy operates as a cognitive mediator of stress reactions. Subjects displayed high epinephrine and norepinephrine secretion on tasks about which they doubted their coping efficacy, but as the strength of their perceived self-efficacy increased, their catecholamine reactivity subsided. Both catecholamines declined suddenly when subjects rejected activities they regarded as exceeding their coping capabilities. These biochemical changes are similar to changes obtained in autonomic reactivity as a function of strength of perceived self-efficacy.

Interestingly, the DOPAC response differs markedly from the other catecholamines at the level of extreme perceived inefficacy. Whereas epinephrine and norepinephrine dropped upon rejection of the task, DOPAC rose to its highest level, even though subjects had no contact whatsoever with the phobic object. DOPAC seemed to be triggered by the mere apperception of task demands overriding perceived deficiencies in coping capabilities.

These findings regarding DOPAC warrant further comment. DOPAC has no known physiological function and arises entirely through the monoamine oxidase mediated degradation of dopamine. Peripheral dopamine is not traditionally thought to play a significant role as either a hormone or a neurotransmitter, although elevation through a variety of stressors has been observed.

Plasma concentrations of free dopamine are very low, typically 1-50 pg/ml. Greater than 95% of dopamine in plasma exists as the sulfate conjugate at the 1-5 ng/ml level. The physiological significance of plasma dopamine sulfate is unclear, but it has been proposed that intraneuronal desulfation may occur, allowing ß-hydroxylation to form norepinephrine. DOPAC might be formed by intraneuronal degradation of free dopamine (after desulfation); thus DOPAC concentrations would parallel those of norepinephrine.

An alternative source of plasma DOPAC could be via central dopamine metabolism. Significant correlations have been described between central dopaminergic activity and plasma DOPAC and homovanillic acid concentrations. These data suggest that under some conditions plasma DOPAC could reflect activity of brain dopamine neurons. Such a central contribution would be consistent with the enhanced DOPAC concentration observed with the perception of inability to cope with a task.

Strengthening perceptions of coping efficacy to maximal level eliminated any differential catecholamine reactivity to the previously intimidating tasks. These findings indicate that the elevated catecholamine secretions observed in the initial primary test resulted from the degree of the perceived match

between coping capabilities and task demands, rather than from properties inhering in the tasks themselves. When self-perceptions are maximized, the tasks elicit equivalent catecholamine responses. That tasks, per se, are not the source of variance in reactivity is further corroborated in other studies using both intergroup and intrasubject designs. Fear and autonomic reactions to coping tasks differ when perceived self-efficacy differs, but reactions to the identical tasks are the same when perceived self-efficacy differs, but reactions to the identical tasks are the same when perceived self-efficacy is raised to the same maximal level. Thus, perceived coping efficacy determines the perceived dangerousness of interactions with phobic objects. People regard contact with phobic objects as potentially dangerous when they believe they cannot control them but regard contact as nondangerous when they believe they can exercise control over them.

Variations in the level of catecholamine secretion during different phases of treatment also provide information bearing on the hormonal concomitants of personal controllability. During the initial phase of treatment, when subjects lacked a sense of controlling efficacy even the mere sight or minimal contact with the phobic object activated catecholamine responses. Curtis and his associates similarly reported elevations of plasma growth hormone levels during brief exposure therapy when phobics had to cope with phobic objects without having been provided strategies for exercising control. However, after subjects gained controlling efficacy in the present study, all three catecholamines dropped to the lowest level, even though subjects were now interacting with the phobic object in the most threatening ways. When all personal control was relinquished, catecholamine reactivity promptly rose. This pattern of results is in accord with a mechanism involving controllability rather than simple extinction or adaptation over time. Others have similarly found that whether or not an intimidating event is stressful to children depends on the amount of control they can exercise over it. Behavioral control decreases fear arousal over and above any benefits derived from predictability of the occurrences of threats.

Autonomic arousal to stressors is reduced by self-knowledge that one can wield control over them at any time even though that controlling capability is unexercised. Choosing not to exercise control at a particular time, but being able to do so whenever one wants to, should be distinguished from relinquished control in which one is deprived of all means of control while subjected to stressors. Relinquished control leaves one completely vulnerable, whereas freely usable control leaves one in full command.

Although the findings from the treatment phase are consistent with the obtained covariations between perceived coping efficacy and catecholamine secretion in the formal tests, the results from the treatment phase must be interpreted with caution. The values were too few to compute statistical significances. Participant modeling served as a vehicle for strengthening self-percepts of efficacy and was not, itself, the subject of study. A nontreated control group was not included because the primary purpose of this research was to test the relation between perceived self-efficacy and catecholamine reactivity, rather than to evaluate a mode of treatment. However, control conditions do not alter phobics' perceived inefficacy or stress reactions, whereas participant modeling is uniformly powerful in instilling a strong sense of coping efficacy.

Systematic investigation of the mechanisms underlying human stress reactions present problems because the stressors created in laboratory situations are often weak, and real-life stressors are usually accompanied by many uncontrolled factors. The phobia paradigm permits the study of one type of intense real-life stressor under controlled laboratory conditions. Powerful treatments provide the means for varying the strength of perceived self-efficacy and for measuring how such changes affect physiological and biochemical responses while coping with the stressor. Such research strategies are well suited for elucidating microrelations between psychosocial influences, cognitive mediators, and the neuroendocrine processes governing stress reactions.

III. MASS SPECTROMETRIC ANALYTICAL NEUROCHEMISTRY

A major focus of our work has been on the improvement of procedures for the study of new, previously unrecognized peptide hormones and neurotransmitters that may be related to stress. Those studies have focused on the use of a new mass spectrometer with fast atom bombardment capability that has just been installed and is fully operative with support from ONR.

In Fast Atom Bombardment (FAB) mass spectrometry, a beam of fast ions and mixtures of fast ions and atoms is used to desorb charged sample molecules and changed fragments of molecules from a liquid surface. This new ionization technique, which is having a major impact on organic mass spectrometry, was developed in England around 1980. The technique grew out of work commenced during the 1960s in which fast ion beams were used to desorb ions from a solid surface (so-called secondary ion mass spectrometry, SIMS). The pivotal contribution f the group in England was to suspend the sample in a liquid matrix (for example, glycerol). This enabled the production of stable ion currents from a wide range of organic molecules, including highly polar and thermally labile species. The ion currents are stable, lasting for several minutes and allowing for statistically accurate data collection which hitherto had not been possible when solid sample surfaces were examined.

Several unique features make the FAB technique the preferred ionization method for mass spectrometry of polar, involatile and thermally labile molecules, including peptides. Interpretation of the resulting spectra is aided by their simplicity, and by the presence of characteristically intense ions in the region of the molecular ion. These are often accompanied by structurally significant fragment ions which result from unimolecular decomposition of the parent molecule. The absence of ions resulting from rearrangement and thermal degradation reactions contribute to the simplicity of the spectra. Additional favorable features of the technique include the simplicity and ease of operation of the ion source.

A comparison of the pattern of peptide fragmentation obtained with a FAB source with that obtained from other methods shows significant differences. Dehydration reactions leading to cyclic intermediates do not appear in the FAB spectra, and the origins of these ions in other spectra are therefore thought to be indicative of thermal degradation prior to ionization. Furthermore, the FAB technique can be used with underivatized peptides. This is another significant advantage of this method over the conventional approaches which

usually require chemical derivatization. Several papers were published through the contract dealing with our efforts to utilize the technique with a quadrupole instrument. However, it is ideally suited to a magnetic sector mass spectrometer.

During the contract our new magnetic sector instrument, with high resolution, high mass capability, was installed. It more than meets specifications and is an instrument of substantial potential which should permit study of new substances in an invaluable manner.

The extended mass range instrument will be used in a wide range of studies primarily involved with peptide identification and characterization. Almost all of these studies have a potential relationship to stress physiology. A goal of this aspect of the work will involve peptides which will have been isolated primarily from adrenal and pituitary sources. Their physiological significance as modulators of the stress response can only be determined after complete characterization of the peptide has been achieved. It is anticipated that the accurate molecular weight data and amino acid sequence information produced by the mass spectrometer will be used in conjunction with data from the peptide sequenator, amino acid analysis and radioimmunoassay data, to achieve complete characterization of each peptide. With the acquisition of the new mass spectrometer, the Laboratory is now ideally set up for these studies.

The instrument was critical to our characterization of a new peptide from the pancreas, pancreastatin. We are now working on techniques which will enhance the sensitivity of mass spectrometry for the study of peptides.

IV. SOCIOPHYSIOLOGY OF SOCIAL RELATIONSHIPS

An exciting direction of the program and of the ONR support was its facilitation of the development of a new area, sociophysiology. Those studies have involved both peripheral and central measurements. The two monographs dealing with sociophysiology which have been published cover much of the work accomplished through the contract dealing with neurophysiological aspects of social behavior and social stress. A series of empirical and review papers have been the product of this part of the program. A key goal of the sociophysiology group is examining the brain-social process relationship. A central aspect of our future work will deal with a fascinating social phenomenon that has had almost no physiological study: stereotyping.

Plasma Catecholamines and Social Environment

As part of the program dealing with sociophysiology, a series of studies have been undertaken dealing with the effects of social-psychological factors on the response to stress utilizing plasma catecholamines as indicators of the stress response. These studies were undertaken utilizing very mild stresses, preferably of a naturalistic nature. Another aspect of the work dealt with electrophysiological measures of social behaviors. That aspect has utilized contingent negative variation for some studies and lateralization measures for others.

A study was undertaken to identify in a human population how the physiological response to stress might be modified by: the immediate environment in which the individual resides; predisposing individual factors; attitudes towards the stressor; the individual's perceived level of social support (which may be viewed as an adaptive resource that facilitates coping); and how successful an individual was at coping with a stressful event or condition. The stress which was used involved blood donation in young adults which provides a naturalistic stress that is mild. The results indicate striking social-psychological factors impacting upon the stress response and also indicate sex differences.

The findings suggest that the immediate social environment has an effect on individuals within that environment. Thus, individuals residing in environments that rank high on instrumental and emotional support tend to excrete lower levels of norepinephrine. Secondly, whether or not an individual perceives a situation as stressful is dependent upon their position in the social structure and their predisposition to high competitive achievement, strong striving for excellence, and a sense of time urgency (Type-A behavior). Thirdly, individuals who perceived higher levels of social support in their living situation tended to be more successful at coping, indexed by lower levels of anxiety. Finally, there were striking sex differences. The stress process appears to operate differently for males and females. Controlling for individual factors, females are more likely to translate their perceptions of stress into feelings of anxiety.

The results emphasize and delineate the importance of social factors in the stress response. This work has already been prepared as a technical report and is now being prepared for publication. The results were extended in a second data collection in which the full range of plasma catecholamines was studied. That work is also being prepared for publication.

Behavioral Studies of Social Stereotyping

We believe the phenomena of social stereotyping is of critical importance. We plan extensive electrophysiological studies in that area but have conducted some behavioral studies in anticipation of physiological measures.

The effect of minimal and full exposure to social stereotypic versus neutral stimuli on observed mood changes was investigated to approach social stereotypes. The association of mood shift and evaluative ratings of elderly categories was also examined. College students viewed slides of elderly females or slides of octagons either very briefly (2 ms) or under adequate viewing conditions (1 s). Subjects' mood was evaluated on anxiety, depression, and hostility, prior to and immediately following the slide presentations. Subsequently, the subjects provided ratings of elderly males and females on the Evaluation, Potency, and Activity dimensions of the Semantic Differential (SD) in response to slides of male and female senior citizens, elder statesmen, and grandmotherly categories. Following the brief exposure, postmanipulative anxiety scores increased significantly. Following exposure to the octagons, the shift in anxiety scores showed a direct and statistically significant positive correlation to Potency ratings. Following exposure to the social stimuli, significant inverse correlations were observed

between change scores on the anxiety and hostility measures and Potency ratings. The elder statesman category received the highest ratings on both Potency and Activity, and the grandmotherly type on Evaluation. The four elderly categories were found to be distinctly located in sematic space. The results are directly relevant to the processing stereotypic information.

Electrophysiological Studies in Sociophysiology

The bulk of recently developed literature that reports electroencephalographic (EEG) data as a dependent variable is often related to illness or abnormality. Even so, it suggests that the technology could be useful in developing explanations of how phenomena such as social comparison, stereotyping, and hierarchical or status behavior occurs; and of how the social situation impacts on brain activity.

There have been very exciting findings to date. Interestingly, in a Navy now made up of both sexes, the two sexes have quite different responses to certain type of social information. One therefore cannot extrapolate from one sex to the other in such studies. For example, whereas we have found that women are more likely to process disagreements with a partner with relatively more activity in the right hemisphere, and agreements with more activity in the left hemisphere, men are more likely to process both agreements and disagreements with relatively more activity from the right brain.

The more complex the organism, the greater the probability that behavior will be preceded by expectations of outcome. Many theories of social behavior, whether based on exchange, consistency or influence, depend upon expectations that presumably are out-of-conscious awareness. We have therefore tried to develop indexes of these prebehavioral responses by monitoring brain activity with the EEG under carefully controlled conditions. Through the efforts supported by the ONR we have now demonstrated the feasibility of this approach. For these studies copies of the shapes used in the "mere exposure" paradigm developed by Zajoncs and Kunst-Wilson were used. We demonstrated that accurate selection of the slides to which the subject had earlier been briefly exposed (below the threshold of conscious awareness) was accompanied by relatively greater right hemispheric activity.

One of our studies investigated the processing of preconsciously acquired information as measured by hemispheric asymmetry. We examined the effects of instruction types upon hemispheric activation and accurate selection of spatial stimuli that were previously presented at a subliminal level. Right-handed females randomly received either an "analytic" or "holistic" instruction. Both groups first saw a series of slides for an extremely brief time (1 ms). Subsequently, these slides were paired with similar but novel slides. One group was asked to view the pairs analytically and to select the one they thought they had seen before. The other group was asked to view the pairs holistically and indicate which of the two they preferred. The results supported the hypothesis that analytic subjects would be more likely to engage the parietal region of their left hemisphere, while holistic subjects would favor relative activation of the right parietal region (Mann-Whitney test, $U = 57$, $p < .04$). An inverse relationship was also detected between parietal laterality and selection accuracy [$r(26) = .39$, $p < .05$]. The findings

suggest that socially presented information can profoundly influence information processing and electrophysiology of the brain.

Our ultimate goals in the sociophysiology program are now directed to the study of the electrophysiology of social stereotyping. It is postulated from psychological studies that face recognition is lateralized to the right cortical hemisphere. We are currently testing that claim with slides of elderly people using the EEG to obtain a real physiological index. In this study, that bears on stereotyping, paper and pencil measures of attitudes, affect and cognitive stereotypes of the elderly also are being taken. The phenomenon of stereotyping has real consequences in terms of social behavior and social stress in an organization such as the Navy. These studies ar designed to initiate investigation of the underlying processes at a sociophysiological level.

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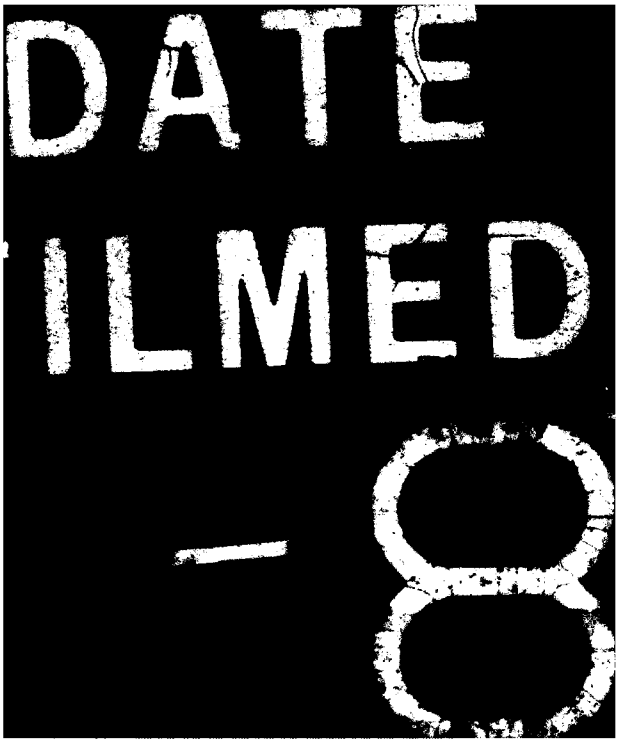
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